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<p>(21) International Application Number: PCT/EP97/01285 (22) International Filing Date: 12 March 1997 (12.03.97) (30) Priority Data: 96/03142 13 March 1996 (13.03.96) FR 60/013,343 13 March 1996 (13.03.96) US (71) Applicant (for all designated States except US): LABORA-TOIRES MERCK SHARP &amp; DOHME-CHIBRET SNC [FR/FR]; 3, avenue Hoche, F-75008 Paris (FR). (72) Inventors; and (75) Inventors/Applicants (for US only): CHASTAING, Gilles [FR/FR]; Laboratoires Merck Sharp &amp; Dohme-Chibret, Route de Marsat, F-63200 Riom (FR). ROZIER, Annouk [FR/FR]; Laboratoires Merck Sharp &amp; Dohme-Chibret, Route de Marsat, F-63200 Riom (FR). (74) Agent: HISCOCK, I. J.; Merck &amp; Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: OPTHALMOLOGICAL COMPOSITION OF THE TYPE WHICH UNDERGOES LIQUID-GEL PHASE TRANSITION</p> <p>(57) Abstract</p> <p>The present invention relates to an ophthalmological composition intended for contacting with the lacrimal fluid wherein said composition is intended to be administered as a non-gelled liquid form and is intended to gel <i>in situ</i>, this composition containing at least one polysaccharide in aqueous solution, of the type which undergoes liquid-gel phase transition gelling <i>in situ</i> under the effect of an increase in the ionic strength of said lacrimal fluid and a pharmaceutically active substance characterised in that said pharmaceutically active substance is pilocarpine or a pharmaceutically acceptable salt thereof, wherein said composition comprises a first component which is an acid aqueous solution of pilocarpine and a second component which is a neutral or alkaline aqueous solution of a polysaccharide of the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength, said components being mixed extemporaneously at the time of first use.</p>		

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TITLE OF THE INVENTION

OPHTHALMOLOGICAL COMPOSITION OF THE TYPE WHICH  
UNDERGOES LIQUID-GEL PHASE TRANSITION

5 BACKGROUND OF THE INVENTION

The present invention relates to an ophthalmological composition containing at least one polysaccharide in aqueous solution, of the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength.

10 They are particularly intended for contacting with lacrimal fluid.

A large percentage of drugs administered to the eye is lost as a result of lacrimal drainage; this applies especially in the case of a liquid formulation. In effect, as a result of this drainage, only a small fraction of the dose administered remains in contact with the cornea for a few  
15 minutes, and an even smaller fraction penetrates into the eye.

To overcome this disadvantage, it is known to use viscous solutions, gels, eye ointments or solid eye implants.

Progress has been made in the delivery of drugs by the use of these galenical forms, especially by using the solid implants, by means of which  
20 it is possible to reduce greatly the doses of active principle in the formulation while retaining a therapeutic response equivalent to that which would be induced by an ophthalmic solution, the latter, in addition, needing to be administered more frequently.

Some of these implants function by diffusion. Thus, for example, in  
25 the "OCUSER<sup>TM</sup>" system, one weekly application of an oval lens in the conjunctival sac enables an active principle to be delivered by diffusion, but this lens has to be removed after use, which is a source of problems for the patients.

Others function by dissolution, and, in this case, since the implants  
30 are either soluble or autodegradable ("LACRISERT<sup>TM</sup>" system), their duration of action is much shorter.

In all cases, the solid implants possess a major disadvantage in that many patients find it difficult to tolerate the introduction into the conjunctival cul-de-sacs of the solid object represented by this implant.

To solve this problem, galenical forms can be used which are liquid  
5 at room temperature and assume a semi-solid form at human body temperature. Such delivery systems are described in US Patent 4,188,373, which propose the use of "PLURONIC™ polyols".

These "PLURONIC™ polyols" are thermally gelling polymers in which the polymer concentration is chosen in accordance with the desired  
10 liquid-gel transition temperature. However, with the commercially available "PLURONIC™ polyols", it is difficult to obtain a gel of suitable rigidity while maintaining the transition temperature at physiological temperatures.

Similarly, Canadian Patent 1,072,413 describes systems where the  
15 gelification temperatures are made higher than room temperature by using additives.

The thermally gelling systems have many disadvantages, including the risk of gelling before administration by an increase in the ambient temperature during packaging or storage, for example.

20 US Patent 4,474,751 of Merck & Co., relates to other systems for delivering drugs based on thermogelification of gels, but these systems require very large amounts of polymers and this is not always well tolerated by the eye.

European patent specification No. 0 227 494-A describes  
25 ophthalmological compositions comprising polysaccharides of the type which undergo liquid-gel phase transition gelling *in situ* under the effect of an increase in the ionic strength of the lacrimal fluid. Specific examples of ophthalmological compositions comprising gellan gum are taught as the basis of ready-to-use solution and, in particular, compositions comprising  
30 the anti-glaucoma agent, timolol.

Pilocarpine is only stable in acid, aqueous solutions (pH <5.0) therefore, in general, conventional pilocarpine ophthalmological compositions are prepared as viscous or non-viscous, ready-to-use solutions at or below pH 5.0. The recommended dosage regimen of such formulations is one to two drops, two to four times a day. In an attempt to provide a sustained release formulation, pilocarpine has been formulated as an aqueous gel. Pilopine HS™ Gel, for example, is an aqueous gel, at pH 4.8, which may be applied once a day. However, gels are difficult to apply and can cause blurred vision. For these reasons, they are less well accepted by patients than solutions.

Whilst the stability of pilocarpine is optimum in aqueous acid solution, the ocular bioavailability and tolerance of the drug are far better at approximately neutral pH. In view of these properties, freeze-dried formulations of pilocarpine which require reconstitution by the patient prior to use have been developed. The pH of the reconstituted formulations is 6.5-6.7. Such formulations, however, suffer from the drawbacks of the necessity for non-sterile reconstitution by the patient. No dual chamber ophthalmic vial exists for freeze-dried products.

Furthermore, due to incompatibility of gellan gum at low pH, pilocarpine cannot be formulated in the manner described in European Patent Specification No. 0 227 494-A as a ready-to-use gellan gum solution.

More recently, a comparison of the ocular penetration of pilocarpine following bilateral instillation of either 1% pilocarpine in 0.6% Gelrite™ or 1% Chibro-Pilocarpine™ (containing 0.325% hydroxyethyl cellulose) has been reported (*Investigative Ophthalmology & Visual Science*, 15 March 1995, Vol. 36, No. 4, S159). The study concludes that the gelling polymer Gelrite™ increases ocular drug bioavailability, but gives no details of the pilocarpine/Gelrite™ formulation.

The present invention relates to an ophthalmological composition intended for contacting with the lacrimal fluid where said composition is

intended to be administered as a non-gelled liquid form and is intended to gel *in situ*, this composition containing at least one polysaccharide in aqueous solution, of the type which undergoes liquid-gel phase transition gelling *in situ* under the effect of an increase in the ionic strength of said  
5 lacrimal fluid and a pharmaceutically active substance characterised in that said pharmaceutically active substance is pilocarpine or a pharmaceutically acceptable salt thereof, wherein said composition comprises a first component which is an acid aqueous solution of pilocarpine and a second component which is a neutral or alkaline aqueous  
10 solution of a polysaccharide of the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength, said components being mixed extemporaneously at the time of first use.

The composition of the present invention, which takes the form of a liquid before its introduction into the eye, undergoes a liquid-gel phase  
15 transition, and hence changes from the liquid phase to the gel phase, once it is introduced into the eye, as a result of the ionic strength of the lacrimal fluid.

This new ophthalmological composition is an advantageous form for several reasons. In particular, since the presence of lacrimal fluid is  
20 required to induce gel formation, any accidental spillage of solution outside of the eye cannot result in gel formation. Furthermore, in contrast to the thermally gelling systems, an increase in the ambient temperature cannot result in the solution gelling during storage.

Also, the polymer used can form a gel at concentrations 10- to 100-  
25 fold lower than those used in systems involving thermogelification. It is hence very well tolerated by the eye.

Following mixing of the two components of the composition, the formulation has the advantage of a pH in the range of 6.5-6.8, and ideally at about pH 6.7, thus providing the optimum conditions for ocular  
30 bioavailability and tolerance of pilocarpine. The bioavailability is further enhanced by the presence of the polysaccharide. Therefore, the

compositions of the present invention which are administered as a drop which then forms a temporary gel layer in the conjunctival sac make it possible to achieve great bioavailability of the pilocarpine at concentrations which are sustained with time.

- 5           Furthermore, in the case of already gelled or semi-solid compositions, it is not possible to administer them by volumetric means, especially when they come from a multi-dose container.

10           The compositions according to the invention have, on the one hand, the advantage of liquid ophthalmic compositions, namely reproducible and accurate dosing, by volumetric means, of the pilocarpine, and on the other hand the advantages known for the systems in rigid or semi-solid gel form, relating to the delivery of active substances.

15           The composition according to the invention consequently has neither the disadvantages of losses of active substances characteristic of simple liquid compositions, nor the unpleasant aspects of solid implant systems, nor finally the difficulties of administration associated with gelled or semi-solid compositions.

20           The aqueous polysaccharide solutions, of the the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength, which are especially suitable according to the invention, are solutions of a polysaccharide obtained by fermentation of a microorganism.

25           Thus, according to the invention, an extracellular anionic heteropolysaccharide elaborated by the bacterium *Pseudomonas elodea* and known by the name gellan gum is preferably used.

30           This polysaccharide, manufactured by Monsanto Performance Materials, is already used as a gelling agent for pharmaceutical compositions, for culture media and also in food products. The structure of this heteropolysaccharide consists of the following tetrasaccharide repeating unit:

→3)-β-D-Glcp-(1→4)-β-D-GlcpA-(1→4)-β-D-Glcp-(1→4)-α-L-Rhap-(1→

which may, or may not, be partially *O*-acetylated on its β-D-glucopyranose (β-D-Glcp) residues.

5           The preparation of such polysaccharides in native and deacetylated form is described, in particular, in US Patent Nos. 4,326,053 and 4,326,052 of Merck & Co., Inc. Rahway N.J., and their structure has been described, in particular, by Jansson & Lindberg, *Carbohydr. Res.* 124 (1983) 135-139.

10           According to the present invention, aqueous solutions containing about 0.1% to about 2.0% by weight of gellan gum, and especially of the product known by the tradename Gelrite™, which is a low acetyl clarified grade of gellan gum, are viscous at low ionic strength but undergo a liquid-gel transition when the ionic strength is increased, and this is the case  
15 when this aqueous solution is introduced into the eye.

          The rigidity of the gel can be modified by adjusting the polymer concentration.

          The gellan gum product not only has the property of changing from the liquid to the gel phase when placed in a medium of higher ionic  
20 strength, but it also possesses the two advantageous additional properties of being thermoplastic and thixotropic which enable its fluidity to be increased by shaking or slightly warming the sample before administration. It will be appreciated that where gellan gum is used, the change from the liquid phase to the gel phase preferably occurs as a  
25 consequence of an increase in ionic strength due to the presence of mono- and divalent cations.

          Applicants have demonstrated gel formation in a rabbit's eye following a 20μl instillation of a solution containing 0.4% by weight of Gelrite™ in deionized water.

30           The present invention relates to the ophthalmic compositions preferably containing about 0.1% to about 2.0% by weight of the



polysaccharide described above, and about 0.01% to about 5% by weight of pilocarpine.

The quantities relating to the aqueous gellan gum solution make it possible to obtain a suitable gel consistency and to compensate the loss induced by the sterilization procedures used during the process of manufacture of these ophthalmic compositions.

In the ophthalmological compositions of the present invention, the first component which is an acid aqueous solution of pilocarpine preferably has a pH in the range of 3.7-4.0.

The second component which is an alkaline solution of a polysaccharide of the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength, preferably has a pH in the range of 9.0-9.5.

Other additives can also take part in the ophthalmic compositions according to the invention. These are, in particular, other polymers suitable for topical application to the eye, small amounts of buffers, acids or bases for adjusting the pH to values suitable for administration to the eye, nonionic tonicity adjusting agents, agents for controlling bacterial contamination or any other additive which assist in the formulation.

One particularly suitable preservative for use in the compositions of the present invention is benzododecinium bromide.

As will emerge in the examples, mannitol can be used in the compositions according to the invention in order to regulate the tonicity of the medium without changing the gelling properties.

Other tonicity adjusting agents can be used, sorbitol or any sugar for example.

For their administration to the eye, the ophthalmic compositions according to the invention are administered in liquid form, by a dual chamber vial such as a vial used for the ophthalmic product, TIMPILO™ (see European Patent Specification No. 0 315 440-A).

The compositions according to the invention can be administered in the usual manner for ophthalmic solutions, in the inferior cul-de-sac of the conjunctiva on the outside of the eye.

By way of example, a drop of liquid composition containing about  
5 25mg of the ophthalmic composition enables about 0.0025mg to about 1.25mg of pilocarpine to be administered.

Toxicological studies prove the good tolerability of gellan gums: acute oral toxicity tests in rats show that the lethal dose 50 (LD<sub>50</sub>) is greater than 5000mg per kg; acute toxicity tests by inhalation show that  
10 exposure of rats for 4 hours to a nominal concentration of 6.09mg/l does not cause the death of any animal in a group of 10 animals, which indicates that the lethal concentration 50 (LC<sub>50</sub>) is greater than 6.09mg/l.

DRAIZE-type eye irritation tests in rabbits show that the product is not regarded as an eye irritant.

15 In the compositions of the present invention, pilocarpine may be used in the form of a pharmaceutically acceptable salt. Particularly preferred salts of pilocarpine are the nitrate and the hydrochloride salts.

Generally, the tears produced by the eye dilute the active substance and very rapidly deplete the dose of active substance administered by  
20 conventional liquid solutions.

The compositions according to the invention containing a polysaccharide in aqueous solution of the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength, are diluted less rapidly and make it possible to obtain a prolonged residence  
25 time which leads to more effective levels of concentration of active substance in the lacrimal film.

The characteristics and advantages of compositions of the present invention are illustrated by the following Examples:

**EXAMPLE 1****FORMULATION**

1% and 2% pilocarpine nitrate are formulated in 0.6% Gelrite Ophthalmic Solution (Tables 1 and 2). In these conditions, the  
5 compositions are instilled as viscous, non-gelled solutions which undergo liquid-gel phase transition in contact with the precorneal tear fluid, in order to improve the ocular penetration of the drug.

Due to the poor stability of the pilocarpine at neutral pH, each of these formulations is constituted by two solutions which have to be mixed  
10 before use:

- A pilocarpine nitrate concentrate at pH 3.70-4.00. This solution corresponds to 25% of the final volume.
- A 0.8% Gelrite solution at pH 9.00-9.50, containing a  
15 tromethamine/maleic acid buffer and mannitol as isotonicizing agent. This solution is a viscous liquid at room temperature and takes 75% of the final volume. It is to be added aseptically to the concentrate to reconstitute the eye drops at the time of dispensing. After mixing, the pH of the solution is in the range of 6.50 to 6.80.

20 The reconstituted solutions are preserved with 0.012% benzododecinium bromide.

It has to be noted that the respective proportions of the concentrate to the diluent are the best compromise between the solubility of the pilocarpine nitrate in the concentrate and the viscosity of the Gelrite  
25 diluent.

**Table 1: 1% Pilocarpine Nitrate/Gelrite Ophthalmic Solution**

<u>Component</u>		<u>Active Concentrate</u>
•	Pilocarpine Nitrate, USP	40 mg
•	Water for Injection, USP qs	1.00 g
		<u>Gelrite Diluent</u>
•	Gelrite (anhydrous)	8.00 mg
•	Mannitol, USP	45.33 mg
•	Tromethamine, USP	2.40 mg
•	Maleic Acid, BP	0.40 mg
•	Benzododecinium Bromide (anhydrous)	0.16 mg
•	Water for Injection, USP qs	1.00 g
		<u>Reconstituted Sol. *</u>
•	Pilocarpine Nitrate, USP	10.00 mg
•	Gelrite (anhydrous)	6.00 mg
•	Mannitol, USP	34.00 mg
•	Tromethamine, USP	1.80 mg
•	Maleic Acid, BP	0.30 mg
•	Benzododecinium Bromide (anhydrous)	0.12 mg
•	Water for Injection, USP qs	1.00 g

\* Based on final volume of 10.0ml (2.5ml of concentrate plus 7.5ml of diluent).

**Table 2: 2% Pilocarpine Nitrate/Gelrite Ophthalmic Solution**

<u>Component</u>		<u>Active Concentrate</u>
•	Pilocarpine Nitrate, USP	80 mg
•	Water for Injection, USP qs	1.00 g
		<u>Gelrite Diluent</u>
•	Gelrite (anhydrous)	8.00 mg
•	Mannitol, USP	29.30 mg
•	Tromethamine, USP	3.00 mg
•	Benzododecinium Bromide (anhydrous)	0.16 mg
•	Water for Injection, USP qs	1.00 g
		<u>Reconstituted Sol. *</u>
•	Pilocarpine Nitrate, USP	20.00 mg
•	Gelrite (anhydrous)	6.00 mg
•	Mannitol, USP	22.00 mg
•	Tromethamine, USP	2.25 mg
•	Benzododecinium Bromide (anhydrous)	0.12 mg
•	Water for Injection, USP qs	1.00 g

\* Based on final volume of 10.0ml (2.5ml of concentrate plus 7.5ml of  
5 diluent).

**EXAMPLE 2****PACKAGING PROCESS**

- The Pilocarpine/Gelrite formulations should be packaged in a dispensing system for packaging separately the two constituents which are mixed in sterile conditions extemporaneously at the time of first use of the system. Examples of such devices are described, for instance, in European patent specification Nos. 0 315 440-A and 0 417 998-A.

**EXAMPLE 3****OCULAR PENETRATION**

The 1% and 2% Pilocarpine/Gelrite Ophthalmic Solutions were tested in ocular distribution studies in the rabbit and compared with the corresponding 0.325% hydroxyethylcellulose (HEC) marketed solutions (Chibro-Pilocarpine™ 1% and 2%).

The pH of the instilled solutions was the same for HEC and Gelrite solutions (close to 6.70).

1/ **1% Pilocarpine Ophthalmic Solutions**

The solutions were tested in the albino and pigmented rabbits:

a. **Albino Rabbit**

Penetrations in the cornea were the same for the Gelrite and HEC vehicles, but were significantly higher ( $p \leq 0.05$ ) at each time point in the aqueous humor and iris + ciliary body for the Gelrite formulations. Ocular bioavailability measured by calculations of the AUC (0-4 hrs) was increased by 2.1 in the aqueous humor and 4.9 in the iris + ciliary body.

b. **Pigmented Rabbit**

Mean Pilocarpine concentrations in cornea, aqueous humor and iris + ciliary body were higher at each time point with Gelrite than with

Chibro-Pilocarpine™ 1%. Ocular bioavailability (AUCs) was increased in the cornea, aqueous humor and iris + ciliary body by 2.0, 2.6 and 1.6, respectively, in favour of the Gelrite formulation.

5    2/    2% Pilocarpine Ophthalmic Solutions

The two solutions were tested in the albino rabbit:

Mean Pilocarpine concentrations in each tissue were always higher with the Gelrite formulation than with Chibro-Pilocarpine™ 2%. AUCs (0-4hrs) were increased in the cornea, aqueous humor and iris + ciliary  
10    body by 2.4, 2.0 and 2.3, respectively, in favour of the Gelrite formulation.

Results obtained in the rabbit show a strong increase in the penetration properties of Pilocarpine when the drug is formulated in a Gelrite vehicle.

15        The values are always higher at each point in the three ocular tissues, except in one experiment where they are similar.

Based on these data, the ocular bioavailability of the Gelrite formulations is on average 2-fold higher than with an HEC vehicle.

CLAIMS:

1. An ophthalmological composition intended for contacting with the lacrimal fluid where said composition is intended to be administered as a non-gelled liquid form and is intended to gel *in situ*, this composition containing at least one polysaccharide in aqueous solution, of the type which undergoes liquid-gel phase transition gelling *in situ* under the effect of an increase in the ionic strength of said lacrimal fluid and a pharmaceutically active substance *characterised in that* said pharmaceutically active substance is pilocarpine or a pharmaceutically acceptable salt thereof, wherein said composition comprises a first component which is an acid aqueous solution of pilocarpine and a second component which is a neutral or alkaline aqueous solution of a polysaccharide of the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength, said components being mixed extemporaneously at the time of first use.

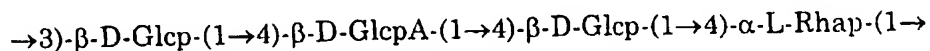
2. A composition as claimed in claim 1 in which the polysaccharide is obtained by fermentation of a microorganism.

20

3. A composition as claimed in claim 2, in which the microorganism is *Pseudomonas elodea*.

4. A composition as claimed in claim 1, in which the polysaccharide has as its basic tetrasaccharide repeating unit:

25



which may, or may not, be partially *O*-acetylated on its  $\beta$ -D-glucopyranose

30 ( $\beta$ -D-Glcp) residues.



5. A composition as claimed in claim 1, which contains about 0.1% to about 2.0% by weight of the said polysaccharide.

6. A composition as claimed in claim 1, which contains 0.01% to  
5 about 5% by weight of pilocarpine.

7. A composition as claimed in claim 6, which contains 1% or 2% of pilocarpine.

10 8. A composition as claimed in claim 1, in which the first component which is an acid aqueous solution of pilocarpine has a pH in the range of 3.7-4.0.

9. A composition as claimed in claim 1, in which the second  
15 component which is an alkaline solution of a polysaccharide of the type which undergoes liquid-gel phase transition under the effect of an increase in the ionic strength has a pH in the range of 9.0-9.5.

10. A composition as claimed in claim 1, in which, following  
20 mixing of the two components of the composition, the formulation has a pH in the range of 6.5-6.8.

11. A composition as claimed in claim 1 which contains in addition one or more other additives selected from other polymers suitable  
25 for topical application to the eye, buffers, acids or bases for adjusting the pH to values suitable for administration to the eye, nonionic tonicity adjusting agents, or agents for controlling bacterial contamination.

12. A composition as claimed in claim 11, in which the agent for  
30 controlling bacterial contamination is benzododecinium bromide.

13. A composition as claimed in claim 11, in which the tonicity adjusting agent is mannitol or sorbitol.

14. A composition as claimed in claim 1 in which the first  
5 component is a pilocarpine nitrate or pilocarpine hydrochloride concentrate at pH 3.70-4.00.

15. A composition as claimed in claim 1, in which the second  
component is a Gelrite™ solution at pH 9.00-9.50, containing a  
10 tromethamine or tromethamine/maleic acid buffer and mannitol.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 97/01285

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 056 420 A (SCHERING CORPORATION) 28 July 1982 see claim 9 see page 3, line 17 - line 22 see page 10, line 15 - page 14, line 9 ---	1-8, 10-14
Y	WO 94 27578 A (PHARMACIA AB) 8 December 1994 see claims 1-3,9,10 see page 4, paragraph 5 -----	1-8, 10-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Information on patent family members

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